REMARKS

Applicant submits herewith a certified copy of the priority application GB 0210397.6 under 37 CFR §1.55. Applicant also submits a supplemental Information Disclosure Statement for the Examiner's consideration.

Following entry of this amendment, claims 1, 3, 4, 6, 7, 9, and new claims 27 and 28 will be pending. Claims 1, 3, 4, 6, and 9 are herein amended. Claims 5 and 14-26 are herein cancelled without prejudice to resubmission in a continuation and/or divisional application. Claims 2, 8, and 10-13 were cancelled previously, without prejudice.

Restriction Requirement

In response to the Restriction Requirement mailed April 24, 2006, Applicant elected to prosecute the claims of **Group I**, e.g., claims 1, 3-7, 9 and 14, drawn to a pharmaceutical composition. Applicant herein cancels without prejudice the claims of Groups II and III (e.g., claims 15-26) directed to nonelected inventions.

Rejections under 35 USC §112

Claims 1, 3-7, 9 and 14 were rejected as allegedly failing to point out and distinctly claim the subject matter of the invention. Specifically, the Examiner asserts that it was

unclear what the ng to μg ranges recited in the claims referred to. The rejection of claim 14 has been obviated by its cancellation.

Applicant has amended claim 1 to define more particularly his invention. As amended, the claim is submitted to be definite. Specifically, as amended the claim is directed to a dosage form (e.g., a sublingual matrix, a patch, or other dosage form as recited, for example, on page 24), which contains between about 0.5 ng to 20 μg desmopressin. This range of active ingredient is submitted to be definite, and to refer to an amount (weight) of active present in a dose intended for administration at a single administration event. Furthermore, the dosage form as now defined must be adapted to be administered via an intranasal, transmucosal, transdermal, conjunctival, or intradermal route. Still further, the dosage form as now defined by the claims must be sufficient to establish in a patient a "steady plasma/serum desmopressin concentration" within the recited low dose range, and be sufficient to decrease urine production. Applicants note further for the record that the phrase "*establishes* in a patient a *steady* . . . *concentration*" means, and is intended to mean, that the concentration of desmopressin in the patient's circulatory system *dwells* for some significant period at one or various concentrations within the recited range so that urine

production is decreased for some period of time, e.g., 4-6 hours (see page 36 of the specification). This is an important limitation as Applicant has discovered that urine production can be decreased in patients with much lower doses of desmopressin than heretofore recognized. Note that the blood concentration range set forth in the claims, per ml, is, *at its highest*, 10 *picograms*, or 0.01 nanogram (0.01 *billionths* of a gram), or 10^{-5} µg. This limitation is not met by a dosage form which delivers desmopressin to induce in the circulation a fleeting desmopressin concentration passing through the recited range while increasing toward a higher concentration during absorption or decreasing from a higher concentration during clearance. As explained in detail in the specification, Applicant has discovered that such low doses are sufficient to decrease urine production yet minimize or eliminate the induction of hyponatrmia.

Support for the added language may be found, for example, in the claims as originally submitted, at page 4 in the Summary of the Invention, and in the description at pages 24 (administration routes- dosage modalities) and page 36 (decrease urine production). Applicant submits that any confusion concerning the metes and bounds of his invention is eliminated by these amendments, and that the 112, second paragraph rejection cannot fairly be applied to the claims as amended.

Applicant requests reconsideration and withdrawal of this rejection.

Rejections under 35 USC §102

The claims in the form previously submitted were rejected as being anticipated by several references outlined in more detail below. Applicant submits that the subject matter of this application as now claimed clearly is not anticipated by any of the cited references, and requests reconsideration and withdrawal of these rejections in view of the amendments and the arguments which follow.

At the outset, Applicant notes the Examiner's position that the "administration of the cited prior art desmopressin pharmaceutical compositions would inherently provide the instantly claimed intended functional effect (i.e., 'establishing a steady state plasma/serum desmopressin concentration' in the instantly claimed picogram ranges)." Applicant might agree with this position if the claims recited that a plasma/serum concentration in the recited range merely had to be *achieved*. However, the claim requires that concentrations within this range must be *established*, that is, maintained for some reasonable time. If it is the examiner's position that the prior art compositions inherently achieve this, that position is incorrect. Desmopressin is a peptide

with notoriously poor bioavailability excepting if administered directly to the blood stream, e.g., intravenously or subcutaneously. As the Examiner has appreciated by a reading of the references, several dosage forms adapted for administration non-intravenously have been developed, but all of these seek to achieve therapeutic blood concentrations well in excess of Applicant's claimed range. Underlying this invention is the discovery that maintenance of such low doses can act effectively to interrupt urine production while decreasing or eliminating induction of hyponatrmia.

Claims 1, 3-7, 9, and 14 were rejected as being anticipated by the Yiv U.S. Patent No. 5,707,648, which discloses a drug delivery composition that can include desmopressin. Yiv discloses a capsule "for oral, rectal, and vaginal, preferably oral and rectal, and more preferably oral," administration. *All claims as amended herein preclude such dosage forms.* Note all claims require that the dosage form be: ". . . adapted for subcutaneous, intranasal, transmucosal, transdermal, conjunctival, or intradermal administration." Furthermore, Yiv discloses that desmopressin is a high priority candidate for incorporation into his oral dosage form, because its known bioavailability is very low. Yiv's purpose is to *increase* oral, rectal and vaginal bioavailability of desmopressin, thus to increase serum plasma concentration over that conventionally

achieved with such dosage forms. This is directly counter to Applicant's teaching that establishment of a *lower* blood concentration is a modality for inducing urine production while avoiding desmopressin's detrimental side effects. As the Examiner notes, in column 16, Yiv discloses a dosage form containing 13 µg of desmopressin for administration to dogs weighing from 9 to 12 kg, but this is an *oral* (capsule) dosage. The examiner notes that at column 17, Yiv discloses a 4 µg dose, but this is for *subcutaneous injection*. There is no recognition in Yiv that temporary reduction in urine volume can be achieved with low dose forms of desmopressin, and no disclosure of its achievement inherently. Note Yiv states at column 16: "the response in Factor VIII levels [Yiv's measure of desmopressin activity] after administration of [desmopressin] at 12 µg /capsule (Table 6C) was not significantly different from levels observed in placebo-treated animals (Table 6D)." Accordingly, Applicant submits that Yiv does not anticipate the subject matter as now claimed.

Claims 1, 3, 5, 7, 9, and 14 were rejected as being anticipated by U.S. Patent No. 6,693,082 to Alonso et al. The lowest dosage of desmopressin Applicant is able to find in Alonzo is 0.3 µg/kg of body weigh, which, for a 70 kg person, would mean about a 20 µg dose. However, the only dosage forms taught by Alonzo appear to be *intravenous*: "after the i.v.

administration", "intravenous administration" and "desmopressin shall be resuspended in the physiological solution, in an adequate amount according to the body weight and shall be administered as a slow endovenous infusion." Applicant can find no suggestion in Alonzo, much less an anticipation, of a dosage form as now claimed, and requests reconsideration and withdrawal of this rejection.

Claims 1, 3, 5, 7, 9, and 14 were rejected as being anticipated by U.S. Patent No. 6,746,678 to Shapiro. Shapiro discloses nasal administration of desmopressin in daily dosages ranging from 10 to 40 micrograms. As Applicant has taught (see paragraph 007 and 008 of the specification) intranasal administration of 5-40 µg desmopressin is conventional, results in a blood concentration of approximately 20-100 pg/mL, and high incidence of hyponatremia. See also paragraph 113:

> "standard intranasal . . . doses of desmopressin produced an unexpectedly high incidence of hyponatremia, a condition in which plasma/plasma/serum sodium falls to abnormally low levels. Hyponatremia can result in seizures, cardiac arrhythmias, cerebral edema and death. The . . . intranasal doses were in the 10 to 20 µg range. While these doses decreased the incidence of nocturia, the hyponatremia suggested that the doses were unnecessarily high resulting in an excessive duration of pharmacodynamic effect on urine concentration with consequent over-hydration and dilutional lowering of plasma/plasma/serum sodium."

Shapiro's nasally administered doses are conventional, do not establish "a steady plasma/serum desmopressin concentration in the range of from about 0.1 picograms desmopressin per mL

plasma/serum to about 10.0 picograms desmopressin per mL" and do not anticipated the subject matter as now claimed herein.

Claims 1, 5-7, and 9 were rejected as being anticipated by U.S. Patent No. 4,863,737 to Stanley et al. Stanley et al. disclose a candy matrix for transmucosal delivery through the mucous membranes of the mouth, pharnyx, and esophagus of drugs, including desmopressin, which can be present in amounts ranging from 10 to 50 micrograms, i.e., a dosage form that, at its lower proposed range, overlaps the amount active required in all pending claims (save new claims 27 and 28). During use of any such dosage form, saliva production and swallowing will vary greatly among patients, varying amounts of the desmopressin active will be transported to the gut (essentially never reaching the blood stream), and some unknown amount will be transported transmucosally into the circulation as Stanley et al suggests.

The disclosure of Stanley et al. does not anticipate the claims as presented herein. To produce an anticipatory embodiment of the Stanley et al. dosage form, one would have to first select desmopressin from the many drugs disclosed, next fix an amount of desmopressin falling within the range required in the claims herein, and next formulate the "candy matrix" so that it delivers desmopressin transmucosally at a rate so as to establish a blood concentration in the recited range. It is

unclear whether this latter achievement is possible with the dosage form described in the reference, but assuming it is, the limitations of Applicant's claims nevertheless clearly do not appear in this reference, and it is woefully deficient as an anticipation. It is well established that to anticipate a claim, a single source must contain all of the elements of the claim. *Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986).

Claims 1, 3-5, 7, and 9 were rejected as being anticipated by Trinh-Trang Tan et al., (J. Am. Soc. Nephrol., 2000, Meeting Abstract), or Wolfson et al. (Am. J. Gastroenterol., 1979) or Jahr et al. (Anesthesia & Analgesia, 1992), or Dixon et al. (British J. Radiol., 1981), or Malan et al. (Toxicol. Methods, 1994) or Tormey et al. (Eur. J. Internal Medicine, 1992). The disclosure of all of these references is limited to some form of intravenous administration, and the desmopressin compositions administered clearly do not meet the limitations of the claims as amended. The rejection should be reconsideration and withdrawn.

Rejections under 35 USC §103

Claims 1, 3-7, 9, and 14 were rejected as being allegedly unpatentable over U.S. Patent No. 5,707,648 to Yiv, in view of

U.S. Patent No. 4,863,737 to Stanley et al. Applicant respectfully traverses the rejection.

Applicant submits that the assessment of obviousness under 35 USC §103 cannot be done merely by comparing the structural elements of the claim with structural elements disclosed in the art, but also requires that the *properties* of a composition be taken into account. The properties and advantages of a chemical composition are part of the "subject matter taken as a whole," that is required to be assessed under section 103. *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963). Applicant submits that the pharmaceutical composition as claimed cannot fairly be rejected as "obvious" because it addresses and solves a problem not so much as appreciated by the applied references, namely, how to safely interrupt urine production in adults, particularly without substantial risk of hyponatremia. It therefore is not surprising that neither Yiv nor Stanley et al. disclose or suggest alone or together a pharmaceutical composition meeting the limitations of any of the pending claims as amended. Neither reference, nor any other reference known to Applicant teach or suggest the use of lower dosages, much less that such lower dosages are effective to interrupt urine production while avoiding hyponatremia. Accordingly, Applicant submits that the subject matter claimed, taken as a whole is not obvious over the combination of Yiv and Stanley et al. within

the meaning of 35 USC §103, and that this rejection to the extent applied to the claims as amended is improper.

If the Examiner has any questions or feels that a discussion with Applicant's representative would expedite prosecution, the Examiner is invited and encouraged to contact Applicant's undersigned representative at the telephone number listed below.

Any fees or credits due with this response may be charged to Deposit Account 23-1665.

Respectfully submitted,

Seymour H. Fein

By Todd E. Garabedian

Todd E. Garabedian, Ph.D.
Registration No. 39,197
Attorney for Applicant

WIGGIN AND DANA LLP
One Century Tower
New Haven, CT 06508

Telephone: (203) 498-4400
Fax: (203) 782-2889

Date: 22 DEC 2006

\12985\2\121770.1